

Progression of Stargardt Disease as Determined by Fundus Autofluorescence Over a 12-Month Period

ProgStar Report No. 11

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IMPORTANCE Sensitive outcome measures for disease progression are needed for treatment trials of Stargardt disease.

OBJECTIVE To estimate the progression rate of atrophic lesions in the prospective Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) study over a 12-month period.

DESIGN, SETTING, AND PARTICIPANTS This multicenter prospective cohort study was conducted in an international selection of tertiary referral centers from October 21, 2013, to February 15, 2017. Patients who were affected by Stargardt disease, aged 6 years and older at baseline, and harboring disease-causing variants of the *ABCA4* gene were enrolled at 9 centers in the United States, United Kingdom, and continental Europe. Data analysis occurred from November 2016 to January 2017.

EXPOSURES Autofluorescence images obtained with a standard protocol were sent to a central reading center, and areas of definitely decreased autofluorescence, questionably decreased autofluorescence, and the total combined area of decreased autofluorescence were outlined and quantified. Progression rates were estimated from linear mixed models with time as the independent variable.

MAIN OUTCOMES AND MEASURES Yearly rate of progression, using the growth of atrophic lesions measured by autofluorescence imaging.

RESULTS A total of 259 study participants (488 eyes; 230 individuals [88.8%]) were examined in both eyes) were enrolled (mean [SD] age at first visit, 33.3 [15.1] years; 118 [54.4%] female). Gradable images were available for evaluation for 480 eyes at baseline and 454 eyes after 12 months. At baseline, definitely decreased autofluorescence was present in 306 eyes, and the mean (SD) lesion size was 3.93 (4.37) mm². The mean total area of decreased autofluorescence at baseline was 4.07 (4.04) mm². The estimated progression of definitely decreased autofluorescence was 0.76 (95% CI, 0.54-0.97) mm² per year ($P < .001$), and the total area of both questionably and definitely decreased autofluorescence was 0.64 (95% CI, 0.50-0.78) mm² per year ($P < .001$). Both progression rates depended on initial lesion size.

CONCLUSIONS AND RELEVANCE In Stargardt disease, autofluorescence imaging may serve as a monitoring tool and definitely decreased autofluorescence and total area as outcome measures for interventional clinical trials that aim to slow disease progression. Rates of progression depended mainly on initial lesion size.

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Autosomal-recessive Stargardt macular dystrophy (STGD1; OMIM: 248200) attributable to disease-causing variants in the *ABCA4* gene is the most common form of juvenile macular degeneration.^{1,2} Although there are no approved therapies available, possible treatment approaches, including pharmacotherapy, gene augmentation therapy, and stem cell therapy, are all in early clinical development.^{2,3} However, the natural history of STGD1 remains poorly characterized, and sensitive, reliable, and clinically relevant outcome measures are needed for clinical trials.⁴ Hence, the retrospective and prospective multicenter Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) studies were launched to characterize the natural history of the disease.⁵ In both studies, the primary outcome measure is the yearly rate of progression of STGD1 as reflected by the growth or the development of atrophic lesions measured by autofluorescence (AF) imaging.⁵ There is precedence of this outcome measure in clinical trials and natural history studies in geographic atrophy secondary to age-related macular degeneration (AMD),^{6,7} especially as regulatory agencies have accepted the growth of atrophy as a primary outcome measure.⁸ While data on the incidence of atrophic lesions and growth rates of such lesions in the retrospective study were previously reported,^{9,10} we present herein the data derived from AF imaging over a 12-month period of the prospective ProgStar cohort.

Methods

The prospective ProgStar study is a multicenter, observational cohort study conducted at 9 centers in the United States, the United Kingdom, and continental Europe. The study design with inclusion and exclusion criteria has been described in detail previously,⁵ and therefore we focus here on key points relevant to AF imaging analysis. Eligible patients had to have at least 2 disease-causing variants in *ABCA4*; however, patients with 1 variant could be enrolled, as long as they had a clinical phenotype typical for STGD1. Further inclusion criteria were a minimum age at the first visit of 6 years or older, a willingness to undergo examinations every 6 months for a 2-year period, and the ability to undergo and perform all examinations. Patients needed to have a well-demarcated lesion of atrophy measuring at least 300 μm and less than 5 standard disc areas (equal to 12 mm^2). The main exclusion criterion was previous or current participation in any interventional study to treat STGD1. The schedule consisted of a baseline visit and 4 planned follow-up visits every 6 months (with a time window for each visit of ± 5 weeks). Relevant patient data including age at enrollment, sex, race, smoking history, and vitamin A supplementation (alone or in multivitamins) were collected. In addition, full-field electroretinograms (ERG) obtained according to International Society for Clinical Electrophysiology of Vision standards¹¹ were recorded once at the baseline visit, or results were submitted if examinations were performed within 5 years of the baseline visit or during follow-up. Electroretinograms were evaluated by the local principal investigators in comparison with the locally healthy cohort es-

Key Points

Question What is the growth rate of atrophic lesions in patients with Stargardt disease?

Findings In this cohort study, the mean progression of definitely decreased autofluorescence lesions was 0.76 mm^2 per year, and the mean progression of the area of total decreased fundus autofluorescence was 0.64 mm^2 per year. Rates of progression depended on initial lesion size.

Meaning The growth rate of atrophic lesions as determined by fundus autofluorescence may be a suitable outcome measure of treatment trials for patients with Stargardt disease.

tablished at each of the participating centers. Scotopic and/or photopic responses were graded as abnormal when amplitudes were reduced or implicit times were delayed.

This analysis used data from the prospective ProgStar study (ClinicalTrials.gov identifier: NCT01977846), which was approved by the Western institutional review board, local institutional review boards, and the Human Research Protection Office of the United States Army Medical Research and Materiel Command. Written informed consent was obtained from each participant or their representative prior to enrollment in the study.

Image Acquisition

The AF imaging protocol in the prospective ProgStar study resulted from a number of considerations.⁵ To prevent possible confounding effects on disease progression by serial imaging in this longitudinal study, short-wavelength, reduced-illuminance autofluorescence imaging created by reducing laser power, as proposed by Cideciyan et al,¹² was implemented in the study design. The detailed acquisition protocol was previously published.⁵ The use of this approach compared with conventional AF imaging with respect to grading results was evaluated in a pilot study, and comparable results were revealed.¹³

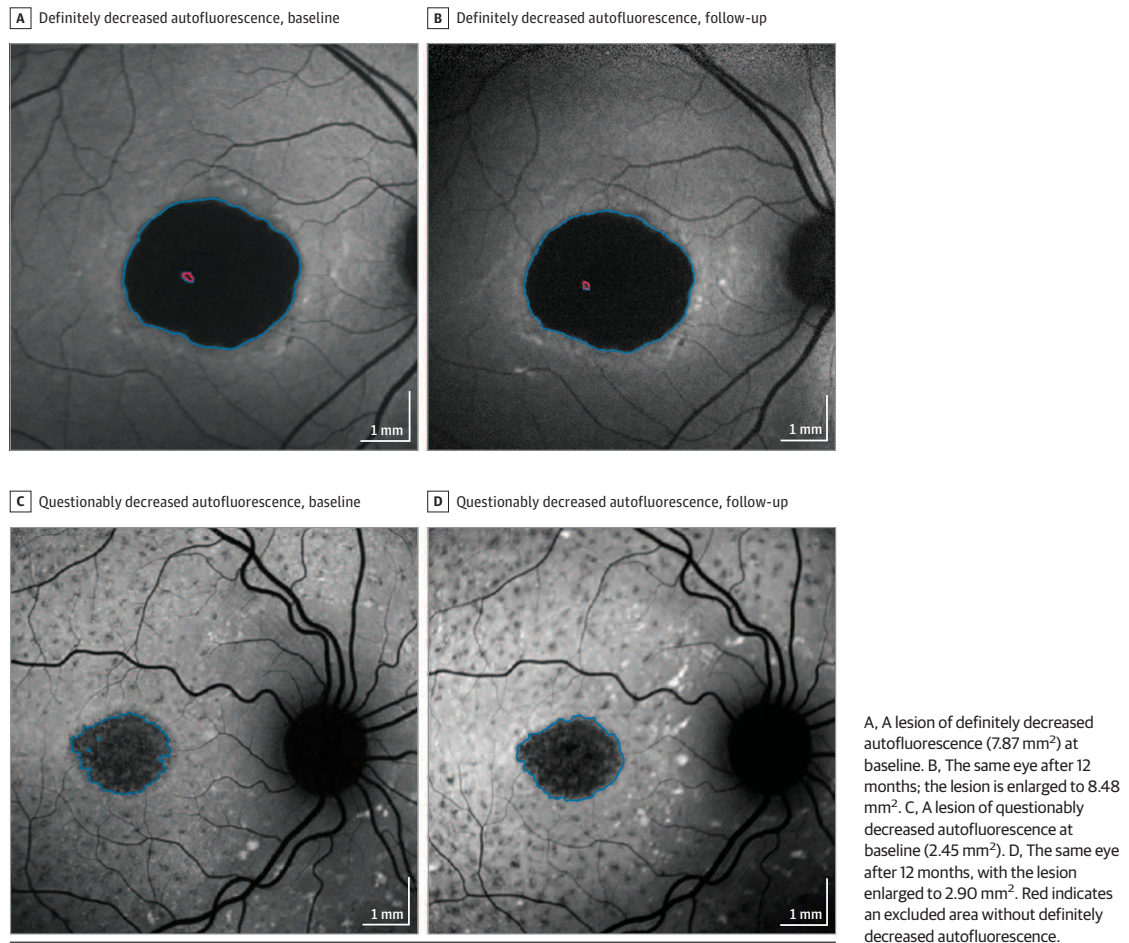
Grading of Atrophic Lesions on Fundus Autofluorescence

The grading protocols applied in the retrospective ProgStar studies were used as previously described in the grading of AF images.^{5,9,13-15} Additional details are available in eMethods 1 in the Supplement.

Qualitative and Quantitative Parameters

Qualitative parameters (as previously published^{9,10,13}) included background heterogeneity, presence of flecks, increased AF at the lesion edge, and the number of lesions of definitely decreased autofluorescence (DDAF). A semiautomated software tool (RegionFinder [Heidelberg Engineering]) was used for quantitatively grading atrophic lesions on AF images, and 2 distinct types of decreased autofluorescence (DAF) were quantified: the level of darkness of an area of DAF was defined qualitatively as definite or questionable, based on its appearance in comparison with blood vessels or the optic nerve head (a reference point for the 100% level of darkness) and the

Figure 1. Examples of Progression of Lesions of Definitely Decreased Autofluorescence and Questionably Decreased Autofluorescence



retinal background seen in the periphery as the opposite reference point (0% blackness; **Figure 1**). The term *definitely decreased autofluorescence* was defined for areas in which the level of darkness was at least 90% in reference to the optic nerve head, while regions with levels between 50% and 90% darkness were termed *questionably decreased AF* (QDAF; **Figure 1**).

Statistical Methods

Statistical methods are provided in eMethods 2 in the [Supplement](#). Linear models with generalized estimating equations were used to estimate the associations of baseline DAF lesion areas with participant characteristics. Longitudinally, linear mixed models with time as the independent variable were used to estimate the yearly change for each outcome. The models include random effects for the intercept and the slope for time, which take into account the potential correlations between eyes and between repeated measurements of the same eye. The rate of lesion area change associated with each variable was first estimated in an univariate analysis. Multivariate analysis was

further run by including variables that were significantly associated with the rate of area change with P values less than .10 in univariate analyses.

Exploratory inspection of lesion growth over time showed a strong dependency on lesion size at the first visit in the retrospective cohort of ProgStar.⁵ For both DDAF and total DAF lesion area, stratified analyses by lesion size at the first visit were performed for eyes with small lesions (ie, $\leq 1.90 \text{ mm}^2$), eyes with intermediate lesions ($>1.9\text{--}5.0 \text{ mm}^2$), and eyes with large lesions ($>5.0 \text{ mm}^2$). All analyses were conducted using SAS version 9.3 (SAS Institute), and P values for 2-sided tests are reported, with those less than .05 considered significant.

Results

A total of 489 eyes of 259 participants (including 230 individuals [88.8%] who were examined in both eyes) were enrolled in the prospective ProgStar study between October 21,

2013, and January 30, 2015. Their mean (SD) age at first visit was 33.3 (15.1) years; 118 (54.4%) were female. The eTable in the Supplement further summarizes the patient characteristics and demographics at the baseline visit.

The AF images were gradable for 480 eyes at the baseline visit. (An image was not available for 1 eye, 5 eyes had ungradable images, and 1 AF image for another eye was captured without following the study protocol.) Of these, AF images were gradable for 447 eyes at the 6-month visit (after excluding 3 ungradable images) and 455 eyes (after excluding 4 ungradable images) at the 12-month visit.

Characteristics of Eyes With DDAF

At the baseline visit, a DDAF lesion was present in 306 eyes (62.3%), with a mean (SD) area of 3.93 (4.37) mm². Flecks were present in 285 eyes and absent in 13 eyes. There was no difference in mean lesion size between the groups. Mean lesion size did also not differ between eyes with unifocal or multifocal lesions. (In eyes with multifocal lesions, this lesion size was the sum of all DDAF lesions.) Eyes with flecks present outside the arcades had significantly larger lesions at baseline (absent, 2.65 [95% CI, 1.91-3.40] mm²; present, 4.81 [95% CI, 3.89-5.73] mm²; $P < .001$), as did eyes with a heterogeneous background (homogenous, 2.58 [95% CI, 1.87-3.29] mm²; heterogeneous, 4.97 [95% CI, 4.03-5.92] mm²; $P < .001$; Table 1). Further baseline characteristics regarding ERG responses (normal, 3.07 [95% CI, 2.40-3.74] mm²; abnormal, 4.75 [95% CI, 3.58-5.92] mm²; $P = .02$) and nonsignificant differences in contiguity of DDAF lesions, smoking history, and use of vitamin A supplementation of these eyes are summarized in Table 1.

Characteristics of Eyes With Any Lesion

The mean (SD) area lesion size of QDAF lesions was 4.07 (4.04) mm². Flecks were present in 424 eyes (88.3%) and absent in 39 eyes (8.1%), and eyes with flecks present had larger lesions than eyes without any flecks (absent, 3.24 [95% CI, 2.37-4.10] mm²; present, 4.37 [95% CI, 3.84-4.90] mm²; $P = .02$); eyes with flecks beyond the arcades also had larger lesions than eyes without flecks (absent, 2.81 [95% CI, 2.32-3.29] mm²; present, 5.81 [95% CI, 4.99-6.64] mm²; $P < .001$; Table 1). Additional characteristics at baseline in eyes with any lesions of DAF are also summarized in Table 1.

Rates of Lesion Progression

In eyes presenting with DDAF at baseline, the rate of DDAF growth was 0.76 (95% CI, 0.54-0.97) mm² per year ($P < .001$). However, growth rates were dependent on initial lesion size (Figure 2): the estimated growth rate in eyes with small lesion sizes (≤ 1.90 mm²) was 0.40 (95% CI, 0.16-0.64) mm² per year; it was 0.72 (95% CI, 0.44-0.99) mm² per year in intermediate-sized DDAF lesions (> 1.90 -5 mm²) and 1.41 (95% CI, 1.10-1.73) mm² per year in large lesions (> 5.0 mm²; Table 2). The estimated difference in the rate of DDAF growth was 0.31 (95% CI, -0.05 to 0.68) mm² per year ($P = .09$) between eyes with smaller lesions and those with intermediate-sized DDAF lesions and 1.01 (95% CI, 0.62-1.40) mm² per year ($P < .001$) between eyes with small and large lesions.

The growth rate of total DAF lesion size overall was 0.64 (95% CI, 0.50-0.78) mm² per year. However, this varied significantly with initial lesion size (Figure 3): for small lesions, the rate was 0.29 (95% CI, 0.10-0.48) mm² per year; for intermediate-sized lesions, the rate was 0.61 (95% CI, 0.43-0.80) mm² per year; and for large lesions, the rate was 1.17 (95% CI, 0.94-1.39) mm² per year (Table 2).

The DDAF and total DAF growth rates were estimated for different subgroups. There were no significant differences in estimated progression rate based on demographic features, including age at baseline, age at onset of symptoms, duration of disease at baseline, smoking status, or vitamin A supplementation (Table 2). There was also no significant difference between subcohorts with normal vs abnormal full-field ERG responses (Table 2). However, the rates of DDAF and total DAF growth were significantly faster in eyes with flecks beyond the arcades compared with eyes without flecks beyond the arcades (DDAF, 0.47 [95% CI, 0.04-0.91] mm²/y; $P = .03$; total DAF, 0.49 [95% CI, 0.21-0.78] mm²/y; $P < .001$) and eyes with heterogeneous backgrounds at baseline compared with eyes with homogenous backgrounds (DDAF, 0.56 [95% CI, 0.13-0.99] mm²/y; $P = .01$; DAF, 0.53 [95% CI, 0.11-0.94] mm²/y; $P = .01$). In eyes with multifocal DDAF lesions (whether alone or in combination with QDAF) at baseline, those with multifocal lesions had faster growth rates compared with eyes with a unifocal DDAF lesion (alone: unifocal DDAF, 0.60 [95% CI, 0.36-0.84] mm²/y; multifocal DDAF, 1.26 [95% CI, 0.82-1.69] mm²/y; $P = .01$; combined with QDAF: unifocal DAF, 0.64 [95% CI, 0.41-0.88] mm²; multifocal DAF, 1.28 [95% CI, 0.86-1.70] mm²; $P = .01$; Table 2).

After applying multivariate models and adjusting for initial lesion size, the difference in growth rates were no longer significant between eyes for absent or present flecks outside the arcades (estimated differences in rate progression: DDAF, 0.09 [95% CI, -0.36 to 0.55]; $P = .69$; DAF, 0.12 [95% CI, -0.26 to 0.50]; $P = .62$) and between eyes with homogenous and heterogeneous background (estimated differences in rate progression: DDAF, 0.17 [95% CI, -0.28 to 0.63]; $P = .46$; DAF, 0.19 [95% CI, -0.20 to 0.59]; $P = .95$). The difference in DDAF growth rates remained significant between eyes with a unifocal lesion of DDAF vs eyes with multifocal lesions of DDAF (estimated rate difference: DDAF, 0.61 [95% CI, 0.23-0.98]; $P = .001$ mm²/y; DAF, 0.54 [95% CI, 0.12-0.96] mm²/y; $P = .01$).

Incidence of DDAF Lesion From Baseline to 12 Months' Visit

There were 174 eyes without any DDAF lesions at baseline, of which 161 (of 163) eyes had gradable images at month 12. At month 12, 43 of 161 eyes (26.7%) had a new DDAF lesion observed, with a mean (SD) lesion size of 1.02 (1.70) mm².

Discussion

ProgStar is, to our knowledge, the first international, multicenter study to evaluate the natural history of STGD1 prospectively and was designed as a hybrid study with a retrospective review of medical records and/or a prospective follow-up of patients.⁵ In this article, we report on ProgStar's primary

Table 1. Association Between Baseline Characteristics and Areas of Definitely Decreased Autofluorescence and Total Area of the Lesions

	Definitely Decreased Autofluorescence at First Visit			Definitely and/or Questionably Decreased Autofluorescence, Combined		
Characteristic	Patients, No. (%)	Area, Mean (95% CI), mm ²	P Value ^a	Patients, No. (%)	Total Area, Mean (95% CI), mm ²	P Value ^b
Eyes, No.	306	NA	NA	480	NA	NA
Demographics						
Age at baseline, y						
<18	47 (15.4)	3.18 (2.22-4.14)	.005	83 (17.3)	4.14 (3.12-5.16)	.003
≥18-<50	194 (63.4)	3.14 (2.48-3.80)		318 (66.2)	3.57 (3.04-4.11)	
≥50	65 (21.2)	6.72 (4.86-8.59)		79 (16.5)	6.72 (5.13-8.31)	
Age at onset of symptoms, y ^c						
<18	130 (42.5)	3.34 (2.58-4.10)	.12	204 (42.5)	3.92 (3.26-4.59)	.36
≥18	153 (50.0)	4.37 (3.33-5.41)		241 (50.2)	4.39 (3.63-5.16)	
Duration of onset of symptoms, y						
≤2	15 (5.3)	1.87 (0.49-3.25)	.13	52 (11.6)	1.80 (1.10-2.50)	<.001
>2-5	37 (13.0)	4.30 (2.19-6.40)		86 (19.1)	3.35 (2.23-4.48)	
>5	233 (81.7)	3.94 (3.21-4.68)		311 (69.3)	4.75 (4.12-5.38)	
Sex						
Male	136 (55.6)	3.57 (2.92-4.21)	.30	267 (55.6)	3.84 (3.26-4.41)	.17
Female	170 (44.4)	4.20 (3.18-5.21)		213 (44.4)	4.51 (3.74-5.29)	
Qualitative autofluorescence grading parameters						
Flecks						
Absent	13 (4.3)	3.65 (2.68-4.61)	.51	39 (8.1)	3.24 (2.37-4.10)	.02
Present	285 (93.1)	3.98 (3.32-4.65)		424 (88.3)	4.37 (3.84-4.90)	
Questionable/ungradable	8 (2.6)	NA		17 (3.6)	NA	
Flecks beyond the arcades ^d						
Absent	124 (40.8)	2.65 (1.91-3.40)	<.001	254 (53.6)	2.81 (2.32-3.29)	<.001
Present	179 (58.9)	4.81 (3.89-5.73)		219 (46.2)	5.81 (4.99-6.64)	
Questionable/ungradable	1 (0.3)	NA	NA	1 (0.2)	NA	NA
Increased autofluorescence at DDAF lesion edge						
Absent	182 (59.5)	4.08 (3.37-4.78)	.81	250 (52.1)	4.43 (3.83-5.03)	.41
Present	82 (26.8)	3.90 (2.51-5.30)		159 (33.1)	4.04 (3.18-4.91)	
Questionable/ungradable	42 (13.7)	NA		71 (14.8)	NA	
Background						
Homogenous	134 (43.8)	2.58 (1.87-3.29)	<.001	274 (57.1)	2.71 (2.24-3.18)	<.001
Heterogenous	172 (56.2)	4.97 (4.03-5.92)		206 (42.9)	6.11 (5.27-6.95)	
No. of lesions of definitely decreased autofluorescence						
Unifocal	233 (76.1)	3.93 (3.29-4.57)	.95	233 (48.5)	5.28 (4.66-5.91)	<.001 ^b
Multifocal	73 (23.9)	3.90 (2.97-4.83)		73 (15.2)	5.28 (4.36-6.20)	
Not present	NA	NA		174 (36.3)	2.19 (1.80-2.58)	
Other						
Vitamin A supplementation						
Yes	39 (12.7)	6.10 (3.59-8.62)	.07	64 (13.3)	5.81 (3.99-7.64)	.06
No	267 (87.3)	3.61 (2.99-4.22)		416 (86.7)	3.96 (3.47-4.46)	
Smoking						
Never	211 (68.9)	3.49 (2.78-4.19)	.12	353 (73.5)	3.88 (3.33-4.43)	.05
Former	55 (18.0)	5.52 (3.77-7.27)		68 (14.2)	4.06 (2.67-5.46)	
Current	40 (13.1)	4.13 (2.21-6.05)		59 (12.3)	6.00 (4.49-7.52)	
Full-field electroretinogram ^e						
Normal	178 (61.8)	3.07 (2.40-3.74)	.02	302 (66.5)	3.44 (2.92-3.97)	.001
Abnormal ^f	110 (38.2)	4.75 (3.58-5.92)		152 (33.5)	5.33 (4.35-6.32)	

Abbreviations: DDAF, definitely decreased autofluorescence; NA, not applicable.

^a Comparisons between subgroups.

^b P value indicates testing for any difference among groups.

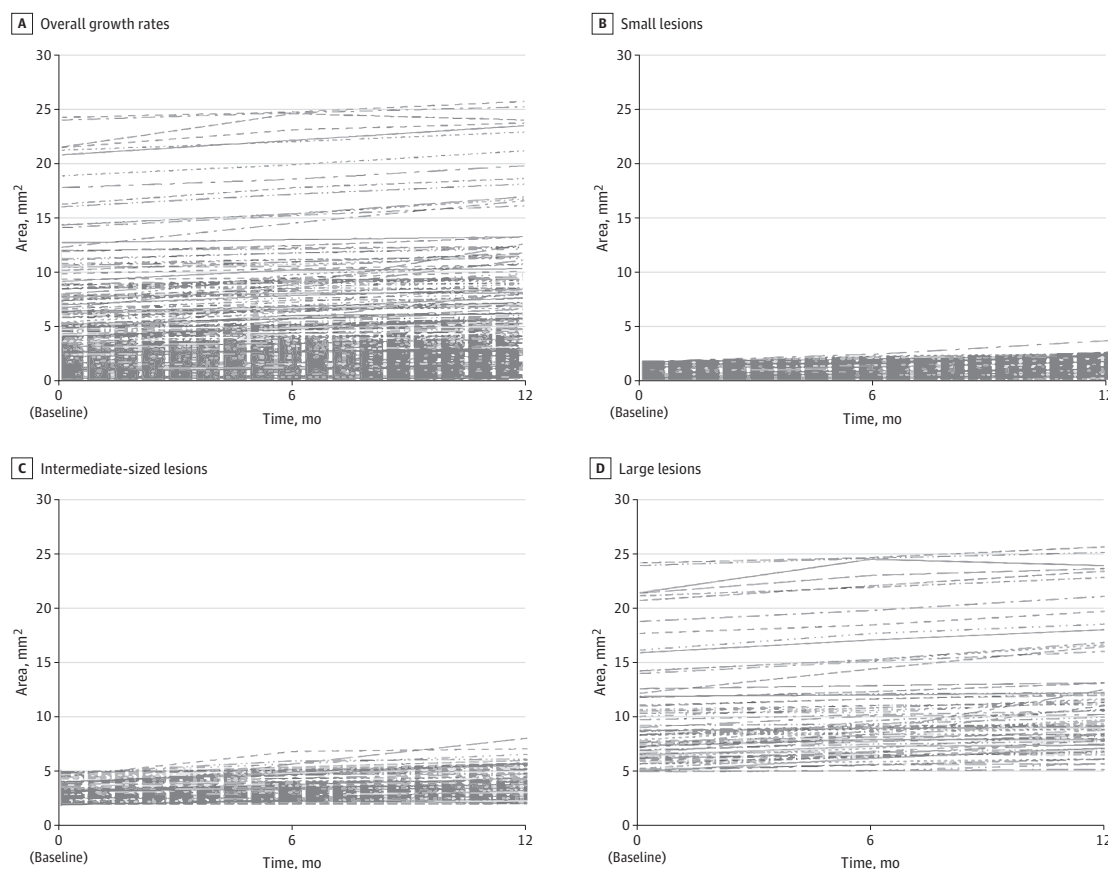
^c Unknown for 21 patients, of whom 2 were asymptomatic (with definitely decreased autofluorescence); unknown for 31 patients, of whom 4 were asymptomatic (with respect to the total area of questionably decreased autofluorescence).

^d The presence of flecks outside the arcades was assessed using information derived from clinical examinations.

^e Not performed at baseline or not available in 24 eyes.

^f Not known for 2 eyes.

Figure 2. Estimated Growth Rates of Lesions of Definitely Decreased Autofluorescence



Estimated growth rates of lesions of definitely decreased autofluorescence are shown as overall growth rates (A) and subgroups of lesion size at baseline: small lesions ($\leq 1.90 \text{ mm}^2$) (B); intermediate-sized lesions ($>1.90\text{--}5 \text{ mm}^2$) (C), and large lesions ($>5.0 \text{ mm}^2$) (D).

outcome measure: namely, the prospective growth rate as determined by AF. Because the lesion growth rate is also characterized by loss of photoreceptors, it is considered a surrogate end point for vision loss.⁸ The estimation of growth rates in STGD1 using AF was first proposed by Chen et al,¹⁶ who observed a mean (SD) rate of $0.94 (0.87) \text{ mm}^2$ per year, and then in multiple reports originating from single centers that suggested a wide range of growth rates, from 0.45 mm^2 per year (in 67 patients [range, $0.06\text{--}4.37 \text{ mm}^2/\text{y}$ for different subgroups])¹⁴ to 1.58 mm^2 per year (range, $0.13\text{--}5.27 \text{ mm}^2/\text{y}$).¹⁷ Of note, all these studies only assessed lesions corresponding to DDAF lesions. The grading protocols of ProgStar also included the grading of QDAF lesions in addition to DDAF lesions, especially as these may represent early stages of disease and may still be rescuable by gene augmentation therapy or pharmacotherapy, for example.^{2,3}

Additionally, short-wavelength, reduced-illuminance autofluorescence imaging was applied in a multicenter setting for the first time. Accumulation of *N*-retinylidene-*N*-retinyethanolamine and lipofuscin are believed to be cyto-

toxic, resulting in dysfunction and cell death of the retinal pigment epithelium (RPE) and photoreceptors. One mechanism is the mediation through blue light-induced damage to RPE cells by photooxidative damage,^{13,18,19} and an increased rate of lipofuscin accumulation and/or its toxicity could be triggered by the high-intensity and short-wavelength excitation light used in conventional AF imaging.¹² A recent comprehensive simulation of photooxidative stress in the RPE in vivo suggested that lipofuscin granules have a 3-fold higher oxygen uptake and light absorption in patients with STGD1 than age-matched control individuals, with the RPE being at increased risk of photooxidative stress, which is amplified by exposure during short-wavelength autofluorescence imaging.²⁰ Furthermore, ophthalmic imaging equipment operates safely below retinal light-damage thresholds; however, those thresholds are mainly based on unaffected retinas, while diseased retinas may have lower light-damage thresholds.^{12,20}

One of the key findings of the analysis of the retrospective medical records review in 215 patients was that growth rates were strongly dependent on initial lesion size and taking

Table 2. Estimates of Yearly Growth Rates for Definitely Decreased Autofluorescence and the Total Area by Baseline Lesion Size and Baseline Characteristics in Univariate Analysis and Multivariate Analysis, After Adjusting for Initial Lesion Size

Baseline Characteristic	Definitely Decreased Autofluorescence (95% CI), mm ² /y			Estimated Rate Difference in Progression per Multivariate Analysis ^a			Definitely and Questionably Decreased Autofluorescence (95% CI), mm ² /y		
	Estimated Progression Rate per Univariate Analysis	Rate	P Value	Estimated Progression Rate per Univariate Analysis	Rate	P Value	Estimated Progression Rate per Univariate Analysis	Rate	P Value
Overall size, mm ²									
≤1.90	0.40 (0.16-0.64)	0.31 (-0.05 to 0.68)	.09	0.18 (-0.20 to 0.57)	.34		0.29 (0.10-0.48)	0.32 (0.05-0.59)	.02
>1.9-≤5.0	0.72 (0.44-0.99)						0.61 (0.43-0.80)	0.14 (-0.37 to 0.65)	.53
>5.0	1.41 (1.10-1.73)	1.01 (0.62-1.40) ^b	<.001 ^b	0.78 (0.36-1.20) ^b	<.001 ^b		1.17 (0.94-1.39) ^b	0.87 (0.58-1.17) ^b	<.001 ^b
Age at baseline, y									
<18	0.71 (0.17-1.24)	-0.07 (-0.67 to 0.53)	.82	NA	NA		0.55 (0.22-0.88)	0.01 (-0.36 to 0.38)	.95
18-50	0.64 (0.37-0.91)						0.56 (0.39-0.74)	NA	NA
≥50	1.13 (0.67-1.59)	0.43 (-0.28 to 1.14) ^c	.24 ^c	NA	NA		1.02 (0.68-1.36)	0.47 (-0.01 to 0.94) ^c	.05 ^c
Age at onset of symptoms, y									
<18	0.57 (0.25-0.90)	0.24 (-0.20 to 0.69)	.28	NA	NA		0.68 (0.36-0.99)	0.18 (-0.25 to 0.61)	.42
≥18	0.82 (0.51-1.13)						0.86 (0.56-1.15)	NA	NA
Duration of onset of symptoms, y									
≤2	1.06 (0.11-2.02)	-0.38 (-1.53 to 0.77)	.51	NA	NA		1.01 (0.10-1.93)	-0.16 (-1.27 to 0.95)	.78
>2-5	0.68 (0.04-1.33)						0.85 (0.23-1.47)	NA	NA
>5	0.71 (0.46-0.96)	-0.35 (-1.33 to 0.63) ^d	.48 ^d	NA	NA		0.77 (0.53-1.01)	-0.24 (-1.19 to 0.70)	.61
Definitely decreased autofluorescence lesions, No.									
Unifocal	0.60 (0.36-0.84)	0.66 (0.16-1.15)	.01	0.62 (0.24-1.00)	.001		0.64 (0.41-0.88) ^e	0.63 (0.15-1.11)	.01
Multifocal	1.26 (0.82-1.69)						1.28 (0.86-1.70) ^e	0.55 (0.13 to 0.97)	.01
Flecks beyond the arcades									
Absent	0.47 (0.14-0.81)	0.47 (0.04-0.91)	.03	0.12 (-0.34 to 0.58)	.61		0.42 (0.23-0.61)	0.49 (0.21-0.78)	<.001
Present	0.95 (0.67-1.23)						0.91 (0.70-1.12)	0.23 (-0.28 to 0.74)	.38
Increased autofluorescence at lesion edge									
Absent	0.82 (0.55-1.10)	-0.13 (-0.63 to 0.36)	.60	NA	NA		0.73 (0.53-0.92)	NA	NA
Present	0.69 (0.28-1.10)						0.51 (0.27-0.75)	-0.22 (-0.53 to 0.09)	.17
Questionable ^f	0.59 (0.00-1.17)	-0.23 (-0.88 to 0.41) ^f	.47 ^f	NA	NA		0.62 (0.25-0.98)	-0.11 (-0.53 to 0.30) ^f	.60 ^f
Background heterogeneity									
Homogenous	0.45 (0.14-0.77)	0.56 (0.13-0.99)	.01	0.20 (-0.27 to 0.66)	.40		0.51 (0.21-0.82)	0.53 (0.11-0.94)	.01
Heterogenous	1.02 (0.73-1.31)						1.04 (0.76-1.32)	0.16 (-0.36 to 0.69)	.54
Vitamin A use									
No	0.72 (0.49-0.95)	0.40 (-0.36 to 1.16)	.31	NA	NA		0.62 (0.47-0.77)	0.13 (-0.34 to 0.60)	.59
Yes	1.12 (0.40-1.84)						0.75 (0.31-1.19)	NA	NA

(continued)

Table 2. Estimates of Yearly Growth Rates for Definitely Decreased Autofluorescence and the Total Area by Baseline Lesion Size and Baseline Characteristics in Univariate Analysis and Multivariate Analysis, After Adjusting for Initial Lesion Size (continued)

Baseline Characteristic	Definitely Decreased Autofluorescence (95% CI), mm ² /y				Definitely and Questionably Decreased Autofluorescence (95% CI), mm ² /y			
	Estimated Progression Rate per Univariate Analysis		Estimated Rate Difference in Progression per Multivariate Analysis ^a		Estimated Progression Rate per Univariate Analysis		Rate Difference per Univariate Analysis	
	Rate	P Value	Rate	P Value	Rate	P Value	Rate	P Value
	Rate	P Value	Rate	P Value	Rate	P Value	Rate	P Value
Smoking								
Never	0.65 (0.41-0.92)		0.37 (-0.20 to 0.94)	.20	NA	NA	0.27 (-0.13 to 0.67)	.19
Former	1.04 (0.53-1.54)				0.85 (0.48-1.22)			NA
Current ^a	0.65 (0.02-1.28)		-0.02 (-0.70 to 0.67) ^a	.96 ^a	0.63 (0.19-1.08)		0.05 (-0.42 to 0.53) ^a	.82 ^a
Electroretinograms								
Normal	0.62 (0.34-0.90)		0.33 (-0.12 to 0.79)	.15	0.58 (0.40-0.76)		0.18 (-0.13 to 0.49)	.26
Abnormal	0.95 (0.59-1.31)				0.76 (0.50-1.01)			NA

Abbreviation: NA, not applicable.

^a After adjusting for initial lesion size in variables associated with lesion growth rate in univariate analysis at significance level of less than or equal to .10.^b Rate difference between eyes with lesions of 190 mm² or less and those with lesions of more than 5.0 mm².^c Rate difference between eyes of patients younger than 18 years and older than 50 years at baseline visit.^d Rate difference between eyes of patients with onset of symptoms less than 2 years ago and those with symptom onset more than 5 years ago.^e Growth rates based on contiguity of definitely decreased area within the total area lesion of decreased autofluorescence.^f Rate difference between eyes with questionable vs absent increased autofluorescence at the lesion edge.^g Rate difference between eyes of those who currently smoke and those who have never smoked.

into account initial size when reporting progression rates (in mm² per year) is important.¹⁰ As previously reported, 145 of 259 patients enrolled in the prospective study had already been followed up retrospectively. Hence, mean (SD) lesion size at baseline in the retrospective study (DDAF, 2.2 [2.7] mm²; DAF, 2.6 [2.8] mm²) was smaller than in the prospective study (DDAF, 3.92 [4.38] mm²; DAF, 4.09 [4.04] mm²). This may be the reason that the estimated mean progression (DDAF, 0.67 [95% CI, 0.44-0.90] mm²/y; DAF, 0.62 [95% CI, 0.47-0.76] mm²/year) was greater in the prospective than in the retrospective study (DDAF, 0.51 [95% CI, 0.42-0.61] mm²/y; DAF, 0.35 [95% CI, 0.28-0.43] mm²/year). One possible explanation could be that a larger initial lesion would have a larger surface area for further growth and thus had a larger rate of growth.

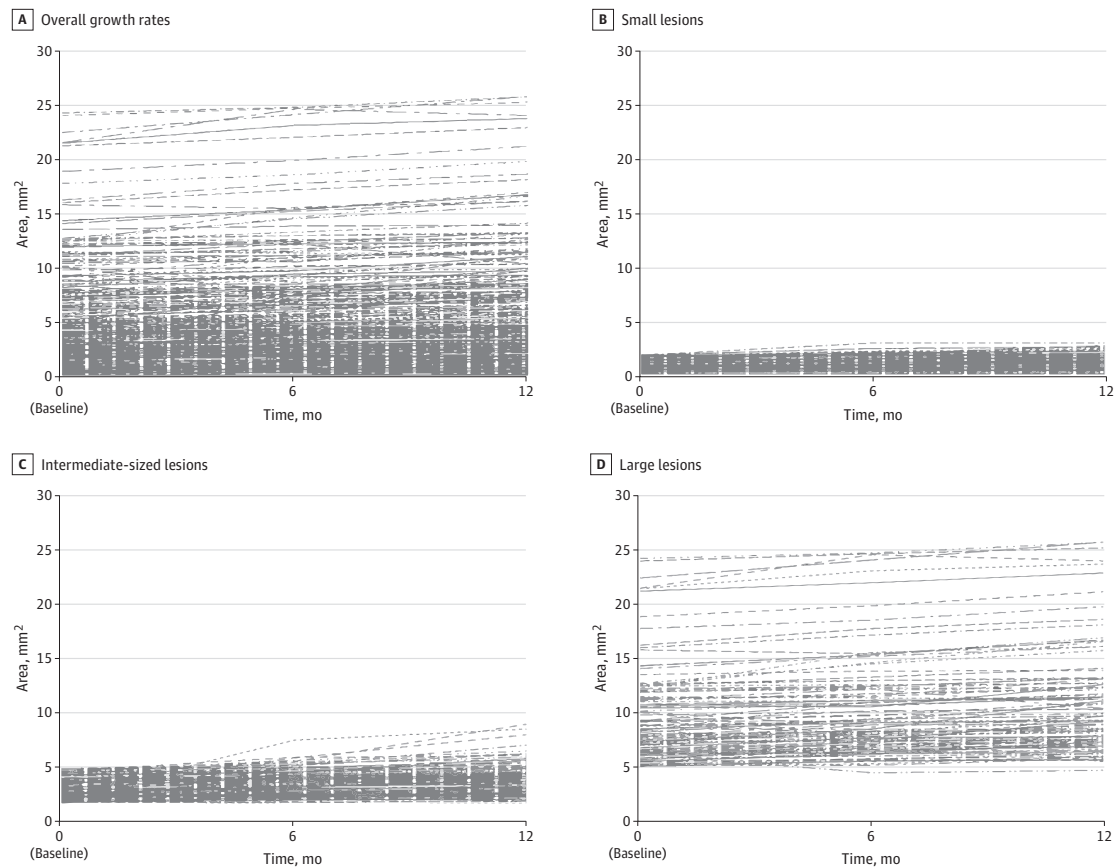
Previous studies from single centers reported slower progression rates for eyes with a homogenous background, although these were not stratified for initial lesion size.^{14,17} A report on the progression of geographic atrophy secondary to AMD showed that the mean change in lesion size from baseline to month 12 was significantly larger in patients who had eyes with multifocal atrophic spots compared with those with unifocal spots,⁷ in keeping with these results on patients with STGD1. There may be shared pathways of both diseases, such as photooxidative stress caused by RPE bisretinoid accumulation and possible links to light exposure in both STGD1 and AMD.²¹ However, STGD1 and AMD clearly differ in atrophy progression, which was recently found to be significantly faster in AMD compared with late-onset STGD1 (ie, cases in which patients are at least 45 years old at self-reported symptom onset).²²

A previous study included electrophysiological assessment and suggested faster progression in patients with abnormal ERGs at baseline; however, the study cohort was very small and did not include genotypic confirmation.¹⁷ We could not detect a significant difference in progression rates between eyes with normal and abnormal responses in full-field ERG, although there was a significant difference in lesion size at baseline; however, there was a numerically higher but nonsignificant faster progression rates in eyes with abnormal ERGs. One possible explanation for this difference with previous work is that ProgStar has some bias, based on its inclusion criteria⁵: to be able to track lesion growth by AF, the maximum lesion size was set to be less than 12 mm², which inevitably lead to the exclusion of eyes with more severe types of STGD1 both genotypically and phenotypically.

This investigation did not analyze genotypes and rates of progression in part because *ABCA4* is a large, complex gene with approximately 1000 disease-causing variants currently reported. Future studies appear warranted regarding a proper genotype-phenotype correlation on progression rates.

The use of vitamin A has potential detrimental effects in patients with disease-causing *ABCA4* mutations, at least based on results derived from animal research.^{23,24} However, 37 of 250 patients (14.3%) took vitamin A in addition to their usual nutrition at baseline; this was surprising, because literally all study investigators advised patients not to take vitamin A supplements. Although we could see a trend toward a faster progression rate in DDAF lesions, this was not significant over a 12-month period.

Figure 3. Estimated Growth Rates of Lesions of Definitely Decreased Autofluorescence Plus Questionably Decreased Autofluorescence Combined



Overall growth rates (A), with subgroups according to lesion size at baseline: small lesions ($\leq 1.90 \text{ mm}^2$) (B); intermediate-sized lesions ($>1.90\text{--}5 \text{ mm}^2$) (C), and large lesions ($>5.0 \text{ mm}^2$) (D).

Limitations

One limitation is the recording of vitamin A intake because a general nutrition diary that would document entire vitamin A intake was beyond the limits of this natural history study. This might be of relevance for upcoming treatment trials for compounds interacting with vitamin A metabolism, however.^{2,3,25}

Smoking has been associated with a myriad of negative ocular effects.²⁶ Recently, subclinical nicotine induced foveal changes in the absence of clinically apparent foveal toxicity in healthy young people who smoked.²⁷ In the limited number of individuals who formerly or currently smoke in this cohort, we did not detect a significant difference in growth rate, at least over the 12-month period. Future studies might potentially explore the possible detrimental outcomes of smoking further.

One essential difference between the retrospective and the prospective study has been the mean observational period. Whereas in the retrospective study, it was 3.9 (1.6) years (range, 0.7–12.1 years), we report herein a follow-up period of 12 months. However, 43 of 161 eyes (26.7%) without a lesion at

baseline developed at least 1 DDAF lesion over these 12 months. In the retrospective study, the median time to develop DDAF lesions was 4.9 (95% CI, 4.3–5.6) years, and by 3.0 years, 24% had developed such a lesion.⁹ This difference in incidence of DDAF lesions can be attributed to the different observational period and the difference in inclusion criteria.

This report provides data on structural changes over a 1-year period, and we cannot determine at this time whether the structural changes correlate with functional changes, such as best-corrected visual acuity and microperimetry-derived retinal light sensitivity.^{28–32} Furthermore, the outcome of genetic variants on disease progression will be explored over a 2-year period.

Conclusions

In conclusion, AF is a suitable tool to track disease progression in STGD1, especially of DDAF lesions. It may be used in interventional trials that aim to slow down disease progression.

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Invited Commentary

Toward a Treatment Trial for Stargardt Disease Putting Out the Fire

Michael A. Grassi, MD

Determining the best outcome measure for a randomized clinical trial of Stargardt disease is complex. Vision, the most commonly used ophthalmic outcome, does not correlate well with the extent of atrophy, changes very little over a 1-year or 2-year period, and, consequently, lacks sensitivity.¹

The purpose of the Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) consortium is to identify a more reliable measure to be used for a therapeutic trial of Stargardt disease. In the present report (ProgStar report No. 11) by Strauss et al,² the investigators specifically seek to characterize



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and delineate the natural history and progression of atrophy in Stargardt disease. Importantly, the US Food and Drug Administration has deemed

progression of atrophy a suitable primary outcome measure for randomized clinical trials.

Using atrophy as an outcome for a randomized clinical trial, though, is not straightforward. In the present ProgStar report, through careful, meticulous work, Strauss et al² specifically identify lesion size and multifocality as 2 key parameters that predict the progression of atrophy. The implications of these findings are nuanced.

First, area of atrophy progresses exponentially. That is, the area of a larger lesion increases at an exponential rate compared with that of a smaller lesion, since the area of a circle depends on the square of its radius. For this reason, a square root transformation has been suggested to account for this effect.³ Without this transformation, faster progression of larger lesions may purely be an artifact of their larger size. Using the square root transformation for atrophic lesions, one can reduce the dependence of progression rates on baseline lesion area. In addition, it is also possible to adjust the analysis based on baseline lesion size. Using either technique or both removes the requirement to stratify on this variable.

Second, not all atrophic lesions are circular. The square root transformation assumes circular atrophic lesions. Noncircular atrophic lesions could introduce a potential confounding effect on a study, as they will progress faster than a circular lesion. Growth rate of atrophy is not only a reflection of size but also a reflection of morphology. The greater the perimeter-to-area ratio of a lesion, the greater its progression rate.

Third, as shown in the study by Strauss et al,² multifocal lesions progress faster than unifocal lesions, even with the

same adjusted area. Multifocal lesions have greater perimeters even at the same surface area, potentially explaining this observation and suggesting that it is also an artifact. Again, the greater the perimeter-to-area ratio, the greater the progression rate in a given eye, regardless of whether the lesions are unifocal or multifocal. Almost 25% of eyes with atrophy in Stargardt disease have multifocal lesions, suggesting that when designing a randomized clinical trial, this factor cannot be overlooked.

The Geographic Atrophy Circularity Index⁴ was developed as a way of attempting to address and mitigate these issues. The index cleverly incorporates more information about the perimeter, as it inherently includes lesion shape, and focality into its calculation. The index is determined by measuring the total perimeter of the lesion(s), then calculating the corresponding size for that perimeter as if the lesion(s) was a perfect circle, and finally comparing the area of that circle with the actual measured area of atrophy. The index correlates inversely with growth rate. The smaller the index, the greater the lesion progression.

By assuming a linear progression rate of atrophy along the perimeter of the retinal pigment epithelium (surrounding the area of atrophy), the Geographic Atrophy Circularity Index correctly puts the focus where it should be: on the border of the lesion.⁵ Hence, spreading atrophy may be like a wildfire in that one should be most concerned with what is still actually burning. Focusing on the border of the atrophy is consistent with clinical experience. Atrophic lesions are more than hypofluorescent areas of dead tissue; they are also hyperfluorescent perimeters of injured or dying cells. In fact, spectral-domain optical coherence tomography reveals that photoreceptors become abnormal along the perimeter before atrophy develops and that there is a leading edge of photoreceptor dysfunction prior to retinal pigment epithelium loss.⁶ Incorporation of findings from spectral-domain optical coherence tomography in the ProgStar cohort may lend increased sensitivity and improved model prediction for progression. Spectral-domain optical coherence tomography could be used to identify earlier signs of atrophy, which might be a more effective juncture for intervention.

There are important implications from the work of Strauss et al² as to how a future randomized clinical trial might be designed. By taking into account the perimeter of atrophic lesions in relation to their area, one can identify a range of lesions that